Future Directions in the Frontline Management of Waldenström Macroglobulinemia

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KEYWORDS

• Waldenstrom's macroglobulinemia • Treatment-naïve • Chemoimmunotherapy
• BTK-inhibitors • Front-line

KEY POINTS

- The ultimate goal of future front-line treatments for Waldenström macroglobulinemia (WM) is to develop therapies that can induce complete remissions, translating into long disease-free intervals and, by this, approaching functional cure in the mostly elderly patient population.
- Future front-line treatments need to be well tolerated and should guarantee a good quality of life in WM, which is indolent in nature and often affects patients with age-associated comorbidities.
- The development of fixed-duration treatment concepts is of high importance as it will ensure better tolerability for the patients and also better cost-effectiveness.
- Future frontline treatments should be accessible worldwide and not limited to Western industrialized countries.

ASYMPTOMATIC PATIENTS

Newly diagnosed Waldenström macroglobulinemia (WM) patients with no significant cytopenias, normal organ functions, and no WM-related symptoms such as hyperviscosity or peripheral neuropathy (smoldering WM) can be safely observed expectantly without compromising their overall survival (OS). Initiation of therapy is contemplated when patients become symptomatic or when hematologic or organ function parameters become significantly altered. Identifying a serum immunoglobin M (IgM) level greater than 4500 mg/dL, greater than 70% bone marrow involvement by lymphoplasmacytic lymphoma (LPL), beta-2 microglobulin greater than 4 mg/dL, and serum albumin less than 3.5 g/dL at diagnosis portends a higher risk of disease progression

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requiring therapy initiation.[1] A model using those parameters identified three risk groups with a median time to progression (TTP) varying between 1.8 and 9.3 years. Furthermore, MYD88 wild-type disease had significantly shorter TTP. This confirms previous evidence that patients with wild-type *MYD88* have more aggressive disease and share genomic alterations with diffuse large B-cell lymphoma (DLBCL).[2–4] Somatic mutations in the C-terminal domain of *CXCR4*, which occur in about 40% of WM,[5] can also affect disease presentation. *CXCR4*-mutated WM tends to have higher serum IgM levels, more bone marrow (BM) infiltration, less nodal involvement field 6, and partial resistance to ibrutinib alone.[6,7] Resistance to zanubrutinib and ixazomib has also been linked to *CXCR4* mutated status.[8,9] Given what we now understand about the existence of WM with distinct prognosis and response to therapy, it is intuitive to ask whether patients with a high risk of early progression or transformation to DLBCL would benefit from early intervention. Ultimately, single cell and immune signatures of tumor evolution in patients with newly diagnosed WM at risk for early progression might shape treatment decisions regarding timing and type of first-line therapy. However, a watch-and-wait approach to WM remains the preferred choice for asymptomatic WM patients.

PATIENTS IN NEED OF TREATMENT

Once indications for treatment initiation are met, the choice of initial therapy requires as much knowledge of each patient's genetic and genomic data as is feasible at the center where the patient is being treated, with the understanding that this information might not be readily available in smaller nonacademic centers.[10] A list of therapy options for treatment-naïve WM is shown in **Table 1**. Except for rituximab monotherapy, all regimens listed provide major response rates (at least partial response [PR]) of 67% or higher, up to 88% in the case of rituximab–bendamustine, versus 40% for rituximab alone. Yet, the rate of very good PR [VGPR] (>90% reduction of IgM levels from baseline, VGPR) is in most cases in the 20% to 35% and often in the single-digit range. Rates of complete response (CR; defined as normal IgM level and complete absence of paraprotein by immunofixation) are rarer and often not achieved at any line of therapy, even with long follow-up and despite achieving deepening of response over time. The lack of satisfactory CR rates observed in WM indicates the presence of subclones with intrinsic drug resistance, for instance, by maintaining IRAK1/IRAK4 activity despite suppression of Bruton Tyrosine Kinase (BTK) or by the emergence of mutated BTK or downstream members of the B-cell receptor (BCR) pathway, as in the case of ibrutinib.[11–14] The persistence of CD20-positive plasma cells is another reason for persistent paraprotein production, even in the total absence of LPL cells in posttreatment biopsies.[15] Attainment of CR matters because, as shown in rituximab monotherapy, it is associated with longer progression-free survival,[16] though it is unclear whether it impacts OS. Intuitively, a combinatorial approach to lymphoma cell survival pathways is the optimal tactic to eradicate the WM clone, obtain higher rates of CRs, and hopefully limit the duration of therapy and extend responses. As single agents, all BTKis require continued exposure for the disease to remain in check.

EMERGING TREATMENTS

There are several new classes of drugs being currently tested in relapsed/refractory WM, which have the potential to move to first-line treatment soon and, with this, to change the treatment landscape for treatment naïve patients with this lymphoma subtype. The non-covalent BTK inhibitor pirtobrutinib has shown remarkable activity in WM patients who failed treatment with covalent BTK inhibitors (cBTKis), mostly

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Table 1
Selected data from prospective studies in treatment-naïve patients with Waldenström macroglobulinemia

Study	Regimen	*N*	PR or Better	VGPR or Better	PFS
Dimopoulos et al,[26] 2007 Kastritis et al,[27] 2015	Dexamethasone Rituximab Cyclophosphamide	72	74%	7%	35 mo (median)
Rummel et al,[28] 2013	Bendamustine Rituximab	257	88%	4%	65 mo (median)
Treon et al,[29] 2009 Treon et al,[30] 2015	Bortezomib Dexamethasone Rituximab	23	83%	35%	66 mo (median)
Dimopoulos et al,[31] 2013 Gavriatopoulou et al,[32] 2017	Bortezomib weekly Dexamethasone Rituximab	59	68%	10%	42 mo (median)
Treon et al,[33] 2014	Carfilzomib Dexamethasone Rituximab	28	68%	36%	46 mo (median)
Castillo et al,[9] 2018 Castillo et al,[34] 2020	Ixazomib Dexamethasone Rituximab	26	77%	19%	40 mo (median)
Buske et al,[35] 2023	Bortezomib Cyclophosphamide Dexamethasone Rituximab	102	81%	17%	81% at 24 mo
	Cyclophosphamide Dexamethasone Rituximab	100	70%	10%	73% at 24 months
Treon et al,[36] 2018 Castillo et al,[37] 2022	Ibrutinib	30	87%	30%	76% at 4 y
Dimopoulos et al,[38] 2018 Buske et al,[7] 2022	Ibrutinib Rituximab	34	76%	27%	70% at 4.5 y
	Rituximab	34	41%	9%	32% at 4.5 y
Tam et al,[8] 2020	Zanubrutinib	19	74%	36%	78% at 42 mo
	Ibrutinib	18	67%	22%	70% at 42 mo
Owen et al,[39] 2020	Acalabrutinib	14	79%	NR	86% at 66 mo

Abbreviations: N, number of patients; NR, not reported; PFS, progression-free survival; PR, partial response; VGPR, very good partial response.
Adapted from Ref.[25]

ibrutinib, in the large Phase 1/2 Bruin trial program. In this trial, pirtobrutinib induced a 66.7% overall response rate in 63 patients previously exposed to cBTKis, with nearly 25% achieving a CR/VGPR and a median PFS of 19.4 months. This encouraging activity was accompanied by an excellent toxicity profile with a very low frequency of $\geq$ grade 3 events except for neutropenia.[17] Of note, $\geq$ grade 3 hypertension and atrial fibrillation occurred in only 2.3% and 1.2% of patients. The BCL2 inhibitor venetoclax has been successfully tested in relapsed/refractory WM in a single arm phase II study; 32 evaluable patients were treated until progression or intolerable side effects. Venetoclax induced a major response rate of 81% and CR/VGPR of 19% with a PFS of 30 months. Of note, activity seemed to be independent of the *CXCR4* mutational status. These data established venetoclax as an attractive compound for the first-line

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treatment of WM. However, the challenge is that despite their encouraging clinical activity, pirtobrutinib and venetoclax as single agents remain a non-fixed duration treatment, similar to the cBTKi. This is a major disadvantage of those emerging treatment concepts inducing cumulative toxicity over time, challenging the patient's compliance, and ultimately causing a substantial financial burden. Thus, there is consensus that the future direction of treatments, particularly in the first-line setting, must move to time-limited treatment.

THE VISION OF FUTURE FRONT-LINE TREATMENT IN WALDENSTRÖM MACROGLOBULINEMIA

Current options for front-line treatment are mainly chemotherapy-based or non-fixed duration, chemotherapy-free cBTKi therapies. How to move on from here? There is consensus that further dose intensification of conventional immunochemotherapy will most likely not succeed and would result in unacceptable toxicity in the mostly elderly population of WM patients. Thus, targeted treatment approaches exemplified by the class of BTKi or venetoclax will potentially act as the backbone of future combination regimens. The next major goal will be to overcome their major limitation of indefinite—duration application. Realistically, this goal will be achieved soon as targeted treatment concepts with different modes of action are already available or tested as single agents in clinical trials. The next logical step to combine these agents, and by doing so to establish chemo-free concepts applied for a defined period, is on the way. In a phase II trial, ibrutinib was combined with venetoclax in 45 treatment naïve WM patients for up to 2 years. Efficacy was impressive, with a 100% overall response rate and 93% major response rate with a short time to major response of 1.9 months. However, the study was prematurely stopped because of unforeseen cardiac toxicity with one grade 4 and two fatal ventricular arrythmia.[18] This illustrates that new combinations must be carefully tested in prospective clinical trials to confirm their feasibility in WM and that we should not extrapolate safety data from related lymphoma subtypes to WM. Toxicity in this trial might result from known off-target effects of ibrutinib. Future trials must confirm that a combination of second-generation cBTKi, such as zanubrutinib or non-covalent BTKi, such as pirtobrutinib, is safe when combined with venetoclax. The combination of venetoclax/rituximab (Ven-R) was highly effective and safe in chronic lymphocytic leukemia.[19] The European Consortium for Waldenström Macroglobulinemia is planning a randomized phase II study comparing 12 months of treatment with Ven-R versus Dexamethasone, Rituximab, Cyclophosphamide (DRC) for six cycles in treatment naïve WM (ClinicalTrials.gov identifier: NCT05099471). In this trial, a timely fixed-duration chemo-free approach is compared with standard immunochemotherapy for the first time, which will help to reevaluate the role of rituximab/chemotherapy in the era of targeted treatments in WM.

Despite these new developments, innovative treatment concepts beyond BTK or BCL2 inhibition are needed. Exciting data about bi-specific anti-CD20/CD3 antibodies were reported in various related B-cell lymphomas, such as follicular lymphoma, DLBCL, and mantle cell lymphoma. These bi-specific antibodies induced deep remissions and encouraging durable remissions in heavily pretreated and refractory patients and are currently tested as single agents or in combination regimens in a variety of clinical trials.[20,21] Chimeric antigen receptor-T cell (CAR-T) cells, retrovirally engineered autologous T cells programmed to attack CD19-positive B cells, have shown tremendous efficacy in relapsed/refractory DLBCL and in follicular lymphoma.[22,23] Studies for both immunotherapy classes are planned or ongoing in WM. These two examples, bi-specific antibodies and CAR-T cells, demonstrate that rapid progress has been made

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in developing innovative treatment concepts which engage the patient's immune system. Data for these approaches in WM are still very limited, and no data exist in treatment naïve WM patients.[24] However, it is conceivable that bi-specific antibodies might move to front-line treatment in WM if data in the relapsed/refractory setting are comparable to their efficacy in follicular lymphoma. Taking it all together, hope is justified that we can offer well-tolerated and highly efficient targeted treatments of fixed-time duration to treatment naïve WM patients shortly, avoiding chemotherapy-associated toxicity and being able to induce functional cure in most WM patients.

AUTHOR DISCLOSURES

C. Buske received honoraria from Roche, Pfizer, Janssen, Hexal, Celltrion, AbbVie, Novartis, Bayer, Morphosys, Regeneron, Beigene; consulting fees from Roche, Pfizer, Janssen, Hexal, Celltrion, AbbVie, Novartis, Bayer, Morphosys, Regeneron, Beigene, Sobi; and Research Funding from Roche, Switzerland, Janssen, United States, Celltrion, South Korea, AbbVie, United States, Bayer, United States, Amgen, United States, and MSD. M.L. Palomba received honoraria from BMS, Kite, Synthekine, and Cellectar.

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